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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/763,175	05/30/2001	Hitoshi Kiyoi	084335/0129	3517

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EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,175	KIYOI ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *24 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *2-4 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,5-9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/30/01*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Election filed September 24, 2004 in response to the Office Action of August 25, 2004 is acknowledged and has been entered. Claims 1-11 are pending in the application and Claims 2-4, 10 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1, 5-9, 11 drawn to a method for screening a candidate compound for an antitumor drug comprising detecting the proliferation of cells in culture and and a candidate compound for an antitumor drug, wherein said compound can be isolated by a method according to the previous claims are currently under prosecution.

2. Applicant's election with traverse of Group 1, claims 1, 5-9, 11 and the species of FDC-P1 is acknowledged. The traversal is on the ground(s) that the Examiner has not provided a true analysis of the claims and has not provided any specific reasons for denying the unity of the claimed invention. This is not the test for unity of invention. The question is do the claims share the same or corresponding special technical features. In this case, the use of animal cells expressing FLT3/ITD is the special technical feature that distinguishes the present invention from the prior art and this feature is covered and shared by claims 1 to 4 and their dependent claims. The argument has been considered but has not been found persuasive. The question is not whether all of the claimed methods share the same corresponding special technical feature, but rather that Applicant is requesting examination of a group larger than a single general inventive entity as defined by PCT procedures. Five different methods of screening are claimed. Applicant clearly delineates these methods as separate embodiments of the present invention on pages 5-6 of the specification. Examiner has found that a single general inventive entity consists of a single screening method and a candidate

compound that could be isolated by the claimed method. As previously set forth, a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. When claims to different categories are present in the application, the claims will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories: (1) A product and a process specially adapted for the manufacture of said product; or (2) A product and a process of use of said product; or (3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or (4) A process and an apparatus or means specifically designed for carrying out the said process; or (5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims of the application will be considered as the main invention in the claims, see PCT article 17(3) (a) and 1.476 (c), 37 C.F.R. 1.475(b) and (d) and all other products and methods will be broken out as separate groups (see 37 CFR 1.475(d).) PCT rules do not include a category which comprises five different methods using a single product. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

It is noted for Applicant's information that the restriction among the three blood cell lines claimed in claim 9 is hereby withdrawn.

3. It is noted that Examiner has established a priority date of May 30, 2001 for the instantly claimed invention pending the translation of the priority document. If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of this priority date for the claimed invention applicant is

invited to submit evidence pointing to the serial number, page and line of a priority document where support, in English can be found establishing an earlier priority date.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claim 9 is rejected under 35 USC 101 because the disclosed invention is inoperative and therefore lacks utility.

Claim 9 is drawn to the method of claim 8 wherein said blood cells include three types of blood cells. The claim is inoperative because none of these blood cell express FLT3/ITD.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 5-9, 11 are rejected under 35 USC 112, first paragraph , because the specification, while being enabling for the claimed method wherein the method is for screening a candidate compound for an anti-myeloid leukemia or an anti-myelodysplasia syndrome drug for patients whose cancers express FLT3/ITD, does not reasonably provide enablement for a method for screening a candidate

compound for an anti-tumor drug. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for screening a candidate compound for an antitumor drug this means screening for drugs for any type of tumor, regardless of whether or not it expresses FLT3/ITD. The specification teaches that the invention relates to a method for screening a candidate compound for a drug against tumors, in particular blood cancers (p. 1, lines 6-10). An objective of the present invention is to elucidate the FLT3/ITD function in blood cancers such as leukemia and to provide a screening method for a candidate compound for a drug against tumors, such as blood cancer, using inhibition of the FLT3/ITD function as an index (p. 3, lines 20-25). Based on experimental observations, the inventors found that inhibition of FLT3/ITD function can be used as an index to screen for a candidate compound for a drug that can be used in the treatment of blood cancers (para briding pages 3-4). FLT3/ITD mutations are found in about 20% of AML patients and about 3% of patients with myelodyspasia syndrome but not in patients with chronic myeloid leukemia or lymphocytic blood cancers (p. 3, lines 5-15). The inventors have found it possible to inhibit aberrant cell growth and to treat tumors including those found in hematopoietic organs, for example leukemia, by blocking the FLT/ITD function (p. 5, lines 24-29). The tumors targeted by the identified drug candidate, screened by the instant method include any tumors caused by internal tandem duplication (ITD) of FLT3 (p. 7, lines 12-17).

One cannot extrapolate the teaching of the specification to the scope of the claims because it appears from the teaching of the specification that the only tumors that are known to be associated with FLT3/ITD are hematological tumors,

specifically acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). The teachings of the specification drawn to the limited association of FLT3/ITD with hematological tumors is confirmed by Serve et al (Int. J. Oncol., 1999, 14(4)765-770) who specifically teach that FLT3/ITD is expressed exclusively in hematopoietic malignancies (see abstract) and by Yokota et al (Leukemia, 1997, 11:1605-1609, IDS item) who specifically teach that FLT3/ITD is completely restricted to AML and MDS, see p. 1605, last paragraph. The specification provides insufficient guidance with regard to these issues and discloses no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention could function as broadly. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

8. The specification is objected to and claim 9 is rejected under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

The claim is drawn to blood cell lines FDC-P1, 32D, BaF.

It is unclear if cell lines FDC-P1, 32D, BaF are known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to a said cell line, it would not be possible to practice the claimed invention. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in

the art could not be assured of the ability to practice the invention as claimed. Exact replication of the claimed cell line is an unpredictable event because the exact constituents of the cell line are unknown and it would require undue experimentation to reproduce the claimed cell line. Deposit would satisfy the enablement requirements of 35 U.S.C. 112, first paragraph. See, 37 C.F.R. 1.801-1.809. Applicant has not disclosed the deposit of said cell lines. If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant"s provision of these assurances would obviate this objection/rejection.

Affidavits and declarations, such as those under 37 C.F.R. 1.131 and 37 C.F.R. 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an

earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

9. Claims 1, 5-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5-9 are indefinite because claim 1 is confusing in reciting in the preamble of the claim "a candidate compound" and referring to "a test sample" in section (b) of the claim. The claim is confusing because it is not clear if the candidate compound and the test sample are one and the same or if there is an additional sample being assayed other than the candidate compound.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –
(b) the invention was patented or described in a printed publication in this or

a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 5-8, 11 are rejected under 35 U.S.C. § 102(b) as being anticipated by Lemola et al (Blood, 1991, 77:1829-1836) as evidenced by Kiyoi et al (Leukemia, 1998, 12:1333-1337) or Teller et al (Leukemia, 2002, 16:1528-1534).

It is noted that, because of the indefinite claim language, that the limitation of a "test sample" recited in claim 1 is interpreted to mean the claimed candidate compound for the purposes of examination.

Kiyoi et al teach that nearly 20% of de novo AML cases, regardless of classification have clinically observed FLT3/ITD (p. 1333, col 2).

Teller et al teach that approximately 20% of AML patients present with FLT3/ITD (p. 1528, col 2).

Kiyoi et al further teach that ITD is a novel modality of somatic mutation which constitutively activates FLT3 wherein the FLT3 is ligand independently phsophsorylated.

The claims are drawn to a method for screening a candidate compound for an antitumor drug comprising providing animal cells showing cytokine-independent proliferation due to expression of FLT3/ITD, contacting said cells with a test sample and culturing said cells in the absence of cytokines, detecting the proliferation of said cells and selecting a compound that inhibits the proliferation of said cells (claim 1), wherein said tumor is a blood cancer (claim 5), wherein said blood cancer is AML (claim 6), wherein said cytokine is IL-3 (claim 7), wherein said animal cells are blood cells (claim 9), a candidate compound for an antitumor drug isolated by said method (claim 11).

Lemoli teach a method for screening a candidate compound for an antitumor

drug, wherein said candidate compounds are Mab195 and 4HC comprising providing primary AML cells, contacting said cells with Mab195 or 4HC (see abstract) and culturing said cells in the absence of cytokines (see p. 1830, col 2), detecting the proliferation of said cells and selecting a compound that inhibits the proliferation of said cells (see p. 1831, cols 1 and 2 and Figure 2), wherein said tumor is a blood cancer, AML, wherein the animal cells are blood cells, wherein the candidate compounds that are isolated/identified by the method are Mab195 and 4HC (see p. 1831, Figure 2), wherein said cytokine is IL-3 (claim 7), wherein said animal cells are blood cells (claim 8), a candidate compound for an antitumor drug isolated by said method (claim 11).

Although the reference does not specifically teach that the animal cells show cytokine-independent proliferation due to expression of FLT3/ITD, given the teaching of both Kiyoi et al and Teller et al that approximately 20% of AML patients present with FLT3/ITD it would be expected that at least a subset of the primary cells tested presented with FLT3/ITD and were therefore cytokine independent. Further, given the teaching of Kiyoi et al that ITD is a novel modality of somatic mutation which constitutively activates FLT3 wherein the FLT3 ligand is independently phosphorylated and the clear teaching of Lemoli et al which demonstrates that the cells proliferate in the absence of cytokines, the claimed method appears to be the same as the prior art method absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from

that taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Although the reference does not specifically teach that the animal cells specifically show independence from cytokine IL-3, given that the cells grow in a cytokine-free environment, it is clear that the cells are independent of all cytokines including IL-3. Given the above, the claimed method appears to be the same as the prior art method absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the method of the prior art does not possess the same material, structural and functional characteristics of the claimed method. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from that taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1, 5-8, 11 are rejected under 35 U.S.C. 103(a) as being unpatentable

over Lemoli et al, Supra as evidenced by Kiyoi et al, Supra, Teller et al, Supra in view of Yokota et al (Leukemia, 1997, 11:1605-1609, IDS item).
It is noted that, because of the indefinite claim language, that the limitation of a "test sample" recited in claim 1 is interpreted to mean the claimed candidate compound for the purposes of examination.

Kiyoi et al teach that nearly 20% of de novo AML cases, regardless of classification have clinically observed FLT3/ITD (p. 1333, col 2).

Teller et al teach that approximately 20% of AML patients present with FLT3/ITD (p. 1528, col 2).

Kiyoi et al further teach that ITD is a novel modality of somatic mutation which constitutively activates FLT3 wherein the FLT3 is ligand independently phsophsorylated.

The claims are drawn to a method for screening a candidate compound for an antitumor drug comprising providing animal cells showing cytokine-independent proliferation due to exprssion of FLT3/ITD, contacting said cells with a test sample and culturing said cells in the absence of cytokines, detecting the proliferation of said cells and selecting a compound that inhibits the proliferation of said cells (claim 1), wherein said tumor is a blood cancer (claim 5), wherein said blood cancer is AML (claim 6), wherein said cytokine is IL-3 (claim 7), wherein said animal cells are blood cells (claim 8), a candidate compound for an antitumor drug isolated by said method (claim 11).

Lemoli et al as evidenced by Kiyoi et al, Teller et al teach as set forth above, the teaching of Lemoli et al differs from the claimed invention only to the extent Lemoli et al do not specifically teach that a subset of the AML primary cells comprise FLT3/ITD,

Yokoto et al teach that 17% of patients with AML present with the FLT2/ITD (p. 1605, col 2) and that this tandem duplication within the domains of FLT3 gene is completely restricted to AML and MDS among a variety of hematological malignancies (p. 1609, col. 1) and further teach an AML-M5 cell line, MOLM-13 with FLT3/ITD (p. 606, col 2).

It would have been *prima facie* obvious at the time the invention was made to have used the cell line of Yokota et al in the method of Lemoli et al in order to screen for a candidate compound for an antitumor drug with a cell type specifically known to encompass a frequent mutation that is completely restricted to AML and MDS. Given the efficacy of the compounds of Lemoli et al in inhibiting proliferation of AML cells, it would be expected that the identified compounds would also inhibit the proliferation of the cell line of Yokota et al.

13. No claims allowed.

14. If applicant disagrees with any rejection set forth in this office action based on examiner's establishment of a priority date May 30, 2001 for the instantly claimed invention, applicant is invited to submit evidence pointing to the serial number, page and line of a priority document where support can be found establishing an earlier priority date, in English.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 872-9306.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

Susan Ungar, PhD
Primary Patent Examiner
December 6, 2004